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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

JUN 27 1997

WARNING LETTER

Certified Mail
Return Receipt Requested

Ms. Monica Case
Responsible Head
Meridian Bio-medical, Inc.
1700 Royston Lane
Round Rock, TX 78664

Dear Ms. Case:

During an inspection of Meridian Bio-medical, Inc. (Meridian), 1700 Royston Lane, Round Rock, Texas, conducted on April 14-21, 1997, FDA inspector/investigators documented significant deviations from Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680 with respect to the manufacture of your products as follows:

1. Failure to establish appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedure include validation of any sterilization process [21 CFR 211.113(b) and 211.110(a)] in that the steam sterilization cycle, i.e., [redacted] used to sterilize stoppers, filling equipment, and production equipment has not been validated. In addition, studies to determine the number and heat resistance of the microorganisms in the stoppers, filling equipment and production equipment have not been performed. (b)(4)

2. Failure to maintain or follow written standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing. and processing to remove pyrogenic properties [21 CFR 211.94(d)] in that the level of endotoxin destruction has not been determined for the parameters used during the validation of dry heat oven [redacted] n addition, the objective of the validation is not clear, since the validation was performed based on the SOP entitled [redacted] and the cycles challenged with endotoxin. (b)(4)

3. Failure to maintain separate or defined areas or such other control systems for operations

as necessary to prevent contamination of other manufacturing areas [21 CFR 211.42(c); 600.10(c)(3); and 600.11(e)(3)] in that:

a. Personnel working in the mold production area were observed moving to the bacteriology and quality control laboratories.

b. There is no assurance that the appropriate air pressure is maintained between the mold production gowning room and the general production hallway.

4. Failure to establish a system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)] in that production and filling areas are not monitored for surface contaminants.

5. Failure to clean, maintain, and sanitize equipment and utensils to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that:

a. Routine testing is not conducted to evaluate the effectiveness of the manual cleaning procedure for filling equipment and glassware. (b)(4)

b. The effectiveness of the cleaning and sanitizing process to remove product and sanitizing agents residues from labware and critical equipment, i.e., [—] bottles has not been established.

c. The water for injection (WFI) holding tank vent filter is not tested for integrity.

6. Failure to test components, drug product containers, or closures that are liable to objectionable microbiological contamination [21 CFR 211.84(d)(6)] in that raw materials undergoing extraction and/or coarse filtration have not been subjected to microbiological tests before use.

7. Failure to establish appropriate time limits for the completion of each phase of production to assure the quality of the drug product [21 CFR 211.111] in that time limits have not been established for refrigerated bulk products.

8. Failure to ensure that all manufacturing steps are performed so that the product will contain only the allergenic and other substances intended to be included in the final product [21 CFR 680.2(a)]. For example:

a. [——] is used as a source material for the manufacture of sardine extract. (b)(4)

b. Studies to demonstrate the absence of [——], e.g., particulate or powder, used during the harvesting procedure of mold mats, has not been performed.

9. Failure to ensure the identity of mold seed cultures [21 CFR 680.1(b)(2)(iii)] in that no documentation was available to demonstrate that the mold source material supplier has submitted and received approval by the Center for Biologics Evaluation and Research of standard operating procedures and testing results of three consecutive lots of a

representative species of mold.

10. Failure to establish and/or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit [21 CFR 211.100] in that:

a. The written procedure entitled [redacted] was not followed in that allergenic product lots 5X19A, 5X34, 6P10, 6Y15, and 6Z13 failed to meet release criteria and the investigations were not conducted. In addition, annual review of product quality standard had not been performed as stated in the SOP.

(b)(4)

b. It was observed that employee practices for aseptic processing technique, and equipment sanitization are inadequate.

11. Failure to maintain or follow written procedures for cleaning and maintenance of equipment [21 CFR 211.67(b)] in that the standard operating procedure (SOP) entitled [redacted] specifies a [redacted] revalidation of the process. However, there is no evidence that the removal of detergent residues has been revalidated since 1992.

12. Failure to establish and/or follow written procedures for the receipt, identification, storage, handling, sampling, and testing of components and drug product containers and closures [21 CFR 211.80(a)] in that there is no procedure describing the flow of materials and product into the filling room.

(b)(4)

13. Failure to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. For example:

a. The basis for the alert and action limits for viable particulate specified in SOPs FP-004 entitled [redacted]" and TP-005 entitled [redacted] is unclear. In addition, alert limits for non-viable particulate monitoring in the production and filling areas are higher than historical data.

b. Retesting procedure used during standardized allergenic extracts lot release is not specified in SOPs TP-023 entitled [redacted]" and TP-026 entitled [redacted]

(b)(4)

c. Air sampling intake tubes used for non-viable particulate monitoring in the aseptic core filling room are not properly placed at or near the actual production activities.

d. The method for Quality Control test sampling of the Water for Injection (WFI) system is not representative of production use.

(b)(4)

e. Conductivity limits are not specified in SOP GP-008 entitled [redacted]

14. Failure of the personnel engaged in the manufacture, processing, packaging, or holding of a drug product to wear clean clothing appropriate for the duties they perform and protective apparel as necessary to protect products from contamination [21 CFR 211.28(a)] in that sterile gowns, e.g., cover suits are worn multiple times in the clean room area before resterilizing them.

15. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair [21 CFR 211.58] in that a hole in the wall was observed in gowning room (Rm. 150).

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the awards of contracts. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

Please notify this office, in writing, within 15 working days of receipt of this letter of the steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include license suspension and/or revocation, seizure, and/or injunction.

Your reply should be sent to my attention in the Office of Compliance, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, HFM-600, Rockville, Maryland, 20852.

Sincerely,

for James Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research